

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ :		(11) International Publication Number:	WO 98/02159
A61K 31/425, 31/44, 31/35	A1	(43) International Publication Date:	22 January 1998 (22.01.98)
(21) International Application Number:	PCT/GB97/01928	(74) Agent:	RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).
(22) International Filing Date:	14 July 1997 (14.07.97)	(81) Designated States:	AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).
(30) Priority Data:		Published	
9614751.7	12 July 1996 (12.07.96)	With international search report.	
9614740.0	12 July 1996 (12.07.96)	Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
9616412.4	5 August 1996 (05.08.96)		
9616409.0	5 August 1996 (05.08.96)		
9616407.4	5 August 1996 (05.08.96)		
(71) Applicant (<i>for all designated States except US</i>):	SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB).		
(72) Inventors; and			
(75) Inventors/Applicants (<i>for US only</i>):	POSTE, George, Henry [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AW (GB). SMITH, Stephen, Alistair [GB/GB]; SmithKline Beecham Pharmaceuticals, New Frontiers Science Park South, Third Avenue, Harlow, Essex CM19 5AD (GB).		

(54) Title: NOVEL TREATMENT OF LEPTINE RESISTANCE

(57) Abstract

A method for the treatment and/or prophylaxis of leptin resistance and/or conditions associated with leptin resistance and/or complications thereof, in humans or non-human mammals, which method comprises the internal administration of an effective, non-toxic and pharmaceutically acceptable amount of a leptin sensitiser or a pharmaceutically acceptable derivative thereof.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav Republic of Macedonia	TM	Turkmenistan
BF	Burkina Faso	GR	Greece	ML	Mali	TR	Turkey
BG	Bulgaria	HU	Hungary	MN	Mongolia	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MR	Mauritania	UA	Ukraine
BR	Brazil	IL	Israel	MW	Malawi	UG	Uganda
BY	Belarus	IS	Iceland	MX	Mexico	US	United States of America
CA	Canada	IT	Italy	NE	Niger	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NL	Netherlands	VN	Viet Nam
CG	Congo	KR	Kenya	NO	Norway	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NZ	New Zealand	ZW	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	PL	Poland		
CM	Cameroon	KR	Republic of Korea	PT	Portugal		
CN	China	KZ	Kazakhstan	RO	Romania		
CU	Cuba	LC	Saint Lucia	RU	Russian Federation		
CZ	Czech Republic	LI	Liechtenstein	SD	Sudan		
DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		
EE	Estonia						

NOVEL TREATMENT OF LEPTINE RESISTANCE

This invention relates to a novel treatment and in particular to a method for the treatment and/or prophylaxis of leptin resistance and/or conditions associated 5 with leptin resistance and/or complications thereof.

Y. Zhang *et al* (Nature, 372, 425-431, 1994) suggest that one of the molecules which plays a key role in energy balance regulation is the *ob* protein. Zhang *et al* also report the cloning and sequencing of both mouse and human *ob* gene protein or 'leptin'.

10 United Kingdom patent application, Publication Number 2292382 relates *inter alia* to polypeptides, OB polypeptides or allelic variants or analogs thereof and their use for modulating bodyweight. In particular, GB 2292382 discloses that OB polypeptides and certain analogs thereof, such as agonists, would be useful for the treatment of obesity.

15 European Patent Application, Publication Number 0306228 discloses certain thiazolidinedione derivatives which are disclosed *inter alia* as having hypoglycaemic and hypolipidaemic activity and activity in treating certain eating disorders.

20 International patent application, Publication number WO 95/25026 also discloses that the compounds *per se* of EP 0306228 are useful for the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. The compound of example 30 of EP 0306228 is 5-(4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl)-2,4-thiazolidinedione (or 'BRL49653').

25 European Patent Applications, Publication Numbers: 0306228, 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740; International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852, also disclose certain thiazolidinedione derivatives 30 which are stated to have hypoglycaemic and hypolipidaemic activity. These compound are also recognised to have insulin sensitiser activity.

35 Another series of compounds generally recognised as having insulin sensitiser activity are those typified by the compounds disclosed in International Patent Applications, Publication Numbers WO93/21166 and WO94/01420. These compounds are herein referred to as 'acyclic insulin sensitisers'. Other examples of

acyclic insulin sensitizers are those disclosed in United States Patent Number 5232945 and International Patent Applications, Publication Numbers WO92/03425 and WO91/19702.

Examples of other insulin sensitizers are those disclosed in European Patent Application, Publication Number 0533933, Japanese Patent Application Publication Number 05271204 and United States Patent Number 5264451.

It is known that the γ -isoform of peroxisome proliferator-activated receptor (herein after PPAR γ) is member of a nuclear receptor superfamily that includes receptors for the steroid, thyroid and retinoid hormones (Evans, Science 240, 889-895, (1988)). It is also known from Chawla *et al* that PPAR γ is expressed early during the differentiation of adipocytes (Endocrinology 135, 798-800, 1994).

It is known from J. Biol. Chem., 270, 12963-12966 that thiazolidinediones such as BRL49653 are PPAR γ agonists.

In a recent publication in the Proceedings of the National Academy of Sciences, [93, (12), 5793-5796 (1996)] Kallen *et al* state that their results indicate that BRL49653 and other antidiabetic thiazolidinediones down-regulate leptin gene expression resulting in lowered plasma leptin concentrations. Kallen *et al* correlate this effect on leptin with the PPAR γ agonist activity of these thiazolidinediones.

In an independent series of experiments using insulin resistant rats, we have found that BRL 49653, has no effect upon leptin expression in the adipose tissue of the rats and, more importantly, that circulating plasma leptin concentrations are significantly lowered. Crucially, this reduction occurs in the absence of food intake and body weight gain leading to the proposal that BRL 49653 and hence other similar compounds must sensitise the target cell in its response to leptin. It follows therefore that BRL 49653 and similar compounds would enhance the anorexic and weight loss effects of leptin and agonists thereof and other agents that amplify cellular responses to leptin. This is considered to be of particular importance for the treatment of those individuals who are unable to respond fully to the leptin signal i.e. who are leptin resistant.

Accordingly, the invention provides a method for the treatment and/or prophylaxis of leptin resistance and/or conditions associated with leptin resistance and/or complications thereof, in humans or non-human mammals, which method comprises the internal administration of an effective, non-toxic and pharmaceutically acceptable amount of a leptin sensitizer or a pharmaceutically acceptable derivative thereof.

In particular, the method comprises the use of a selective leptin sensitiser.

Suitably, the leptin sensitiser is administered in combination with leptin and/or an analogue, such as an agonist, thereof. Thus in one favoured aspect, the method comprises the co-administration of an effective, non-toxic and

- 5 pharmaceutically acceptable amount of a leptin sensitiser and leptin and/or an analogue, such as an agonist, of leptin.

Leptin resistance gives rise to obesity and disordered control of food intake and energy expenditure.

Conditions and complications associated with leptin resistance include

- 10 cardiovascular diseases especially atherosclerosis, impaired glucose tolerance and non-insulin dependant diabetes.

In one particular aspect, the present invention provides a method for the treatment and/or prophylaxis of obesity in humans or non-human mammals, which method comprises the internal administration of an effective, non-toxic and

- 15 pharmaceutically acceptable amount of a leptin sensitiser or a pharmaceutically acceptable derivative thereof.

Preferably the obesity is associated with or is caused by leptin resistance.

The method is also of particular benefit to patients suffering from the insulin resistant diabetes syndrome, including the pre-diabetic impaired glucose tolerance phase of the syndrome. Prophylaxis is of particular benefit in the pre-diabetic, impaired glucose tolerance phase of the syndrome.

A suitable leptin sensitiser is an insulin sensitiser, including thiazolidinedione and acyclic insulin sensitisers.

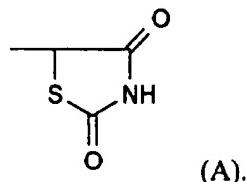
A suitable leptin sensitiser is a PPAR γ agonist.

- 25 Suitable PPAR γ agonists include thiazolidinediones.

A particular leptin sensitiser is that which has both insulin sensitiser and PPAR γ agonist activity.

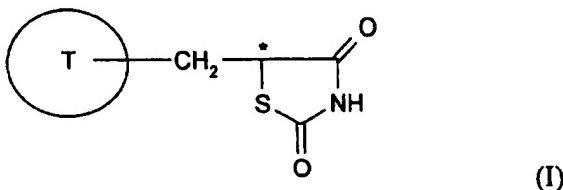
A suitable thiazolidinedione is a thiazolidine-2,4-dione derivative, that is a compound comprising a moiety of formula (A):

30



Suitable compounds comprising a moiety of formula (a) include compounds of formula (I):

5



or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein T represents an aryl or

10 heterocyclyl group optionally substituted with one or more alkyl groups, aralkyl groups or heterocyclylalkyl groups, the said alkyl, aralkyl and heterocyclylalkyl groups themselves being optionally substituted.

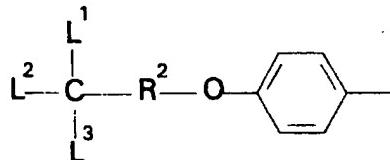
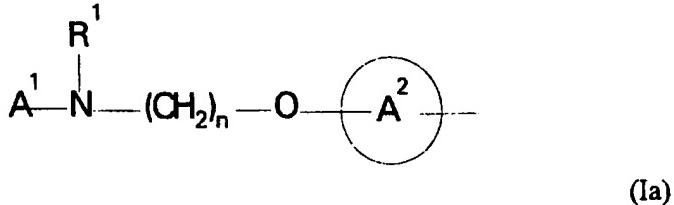
Suitably, the carbon atom marked with an asterisk (*) in formula (I) is a chiral carbon.

15 Suitably, T represents a moiety selected from the list consisting of (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig), (Ih), (Ii), (Ij), (II), (Im), (In), (Io) and (Ip):

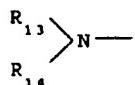
20

wherein A¹, A², R¹ and n are as defined below and in relation to formula (I) of EP 0306228; or

25

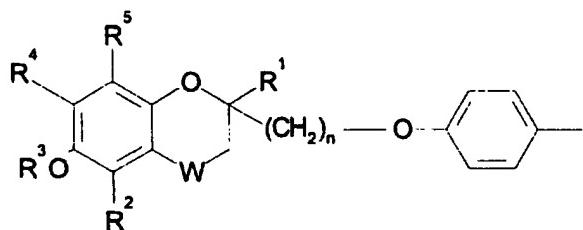


- wherein L₁ and L₂ are the same or different and each represents hydrogen or lower alkyl or L₁ and L₂ are combined to form an alkylene group;
- L₃ is substituted or unsubstituted alkyl, alkoxy, cycloalkyl, phenylalkyl, phenyl, aromatic acyl group, a 5-or 6-membered heterocyclic group including 1 or 2
- 5 heteroatoms selected from the group consisting of nitrogen, oxygen, and sulphur, or a group or the formula



- wherein R₁₃ and R₁₄ are the same or different and each is lower alkyl or R₁₃ and R₁₄ are combined to each other either directly or as interrupted by a heteroatom selected
- 10 form the group consisting of nitrogen, oxygen or sulphur to form a 5- or 6-membered ring;
- R₂ is a bond or a lower alkylene group or a pharmaceutically acceptable salt thereof (providing compounds as defined in EP8203); or

15

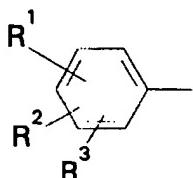


(Ic)

- wherein R¹, R² are the same or different and each represents a hydrogen atom or a C₁₋₅ alkyl group;
- 20 R³ represents a hydrogen atom a C₁₋₆ aliphatic acyl group, an alicyclic acyl group, an aromatic acyl group, a heterocyclic acyl group, an araliphatic acyl group, a (C₁₋₆alkoxy)carbonyl group, or an aralkyloxycarbonyl group;
- R⁴ and R⁵ are the same or different and each represents a hydrogen atom, a C₁₋₅ alkyl group or a C₁₋₅ alkoxy group, or R⁴ and R⁵ together represent C₁₋₄ alkylenedioxy
- 25 group;
- n is 1,2 or 3;
- W represents a -CH₂->CO, or CH-OR⁶ group (in which R⁶ represents any one of the atoms or groups defined for R³ and may be the same as or different to R³) and

Y and Z are the same or different and each represents an oxygen atom or an imino(=NH) group; and pharmaceutically acceptable salts thereof, (providing compounds of formula (I) as defined in EP 0139421); or

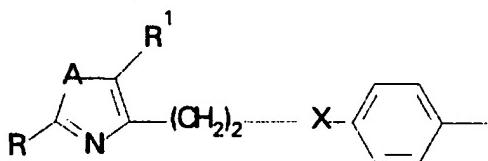
5



(Id)

wherein R¹, R² and R³ are as defined in relation to formula (I) of EP 0032128; or

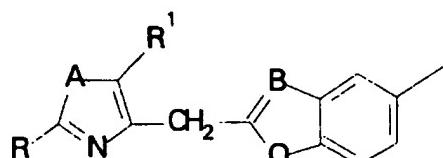
10



(Ie)

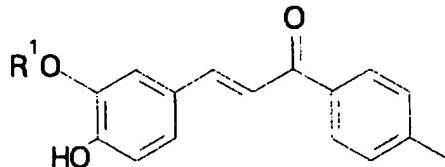
or a pharmaceutically acceptable salt thereof, wherein R is cycloalkyl of three to seven carbon atoms, naphthyl, thienyl, furyl, phenyl, or substituted phenyl wherein
15 said substituent is alkyl of one to three carbon atoms, alkoxy of one to three carbon atoms, trifluoromethyl, chloro or bis(trifluoromethyl);
R¹ is alkyl of one to three carbon atoms;
X is O or C=O;
A is O or S; and
20 B is N or CH;
(providing compounds as defined in relation to formula (I) of EP 0428312); or

25



(If)

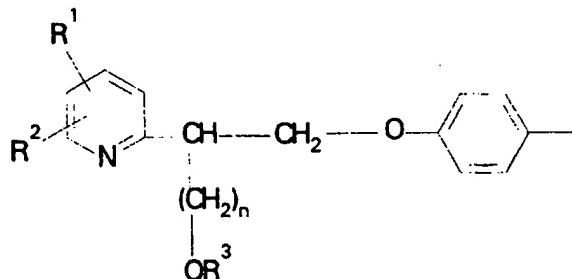
wherein A, B, R and R¹ are as defined in relation to formula (Ie) above and in relation to formula (II) of EP 0428312; or



5

(Ig)

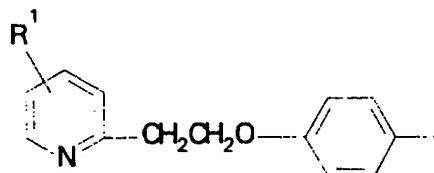
wherein R¹ is as defined in relation to formula (I) of EP 0489663; or



10

(Ih)

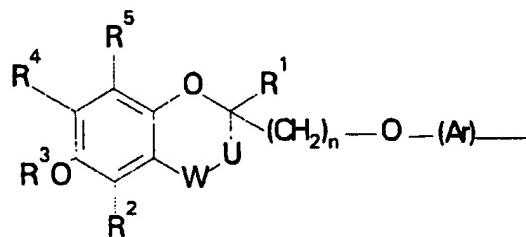
wherein R¹, R², R³ and n are as defined in relation to formula (I) of EP 0155845; or



15

(Ii)

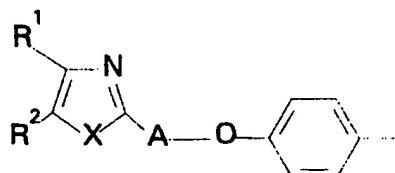
when R¹ is C₁₋₆ alkyl, especially ethyl, as defined in EP 0257781; or



(Ij)

wherein Ar, R¹, R², R³, R⁴, R⁵, n, U and W are as defined in relation to formula (I) of United States Patent No. 5104888; or

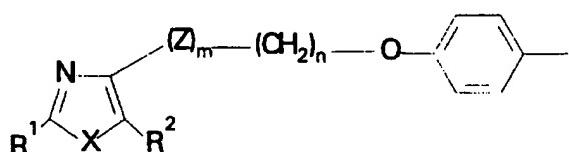
5



(Ik)

when A, R¹, R² and X are as defined in relation to formula (I) of EP 0208420; or

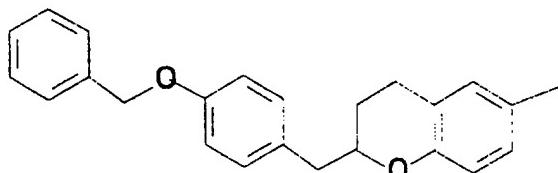
10



(II)

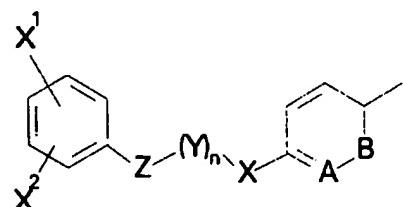
when R¹, R², X, Z m and n are as defined in relation to formula (I) of EP 0177353; or

15



(Im)

20 according to formula (I) of EP 0319189; or



(In)

wherein A and B each independently CH or N, with the proviso that when A or B is N, the other is CH;

5 X is S, SO, SO₂, CH₂, CHO or CO;

n is 0 or 1;

Y₁ is CHR₂₀ or R₂₁, with the proviso that when n is 1 and Y₁ is NR₂₁, X₁ is SO₂ or CO;

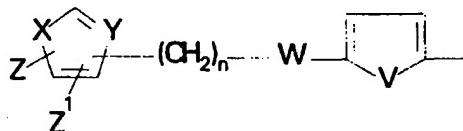
Z is CHR₂₂, CH₂CH₂, CH=CH, 

10 OCH₂, SCH₂, SOCH₂ or SO₂CH₂;

R₁₉, R₂₀, R₂₁ and R₂₂ are each independently hydrogen or methyl; and

X₂ and X₃ are each independently hydrogen, methyl, trifluoromethyl, phenyl, benzyl, hydroxy, methoxy, phenoxy, benzyloxy, bromo, chloro, or fluoro; or a pharmaceutically acceptable cationic salt thereof,

15 or a pharmaceutically acceptable acid addition salt thereof where A or B is N, (providing compounds as defined in relation to formula (I) of EP 0332331); or



(Io)

20

wherein V is -CH=CH-, -N=CH-, -CH=N- or S;

D is CH₂, CHO, CO, C=NOR₁₇ or CH=CH;

X is S, O, NR₁₈, -CH=N or -N=CH

Y is CH or N;

25 Z is hydrogen, (C₁₋₇)alkyl, (C₁₋₇)cycloalkyl, phenyl, naphthyl, pyridyl, furyl, thienyl, phenyl, mono- or disubstituted with the same or different groups which are(C₁₋₇)alkyl, trifluoromethyl, (C₁₋₃)alkoxy, fluoro, chloro or bromo;

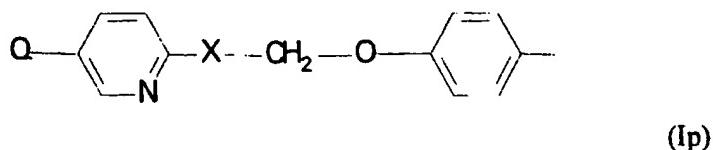
Z₁ is hydrogen or (C₁₋₃)alkyl;

R₁₇ and R₁₈ are each independently hydrogen or methyl; and n is 1,2 or 3;

30 or a pharmaceutically acceptable cationic salt thereof,

or a pharmaceutically acceptable acid addition salt thereof when the compound contains a basic nitrogen, (providing compounds as defined in relation to formula (I) of EP 0332332; and

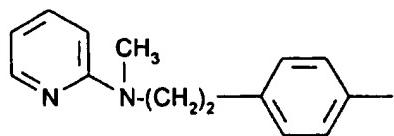
5



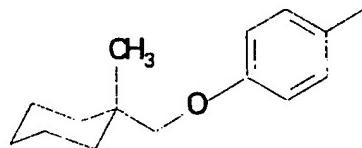
wherein Q and X are as defined in relation to formula (I) of International Application No. WO 92/18501.

10 Favourably, T represents a moiety of the above defined formula (Ia), (Ic), (Ie), (If), (Ii), (Ik), (Im) or (Io).

In particular T represents a moiety selected from the list consisting of (a), (b), (c), (d), (e), (f), (g), (h) and (i):

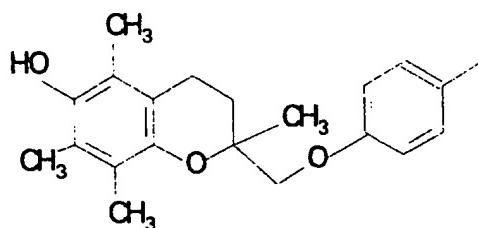


(a)

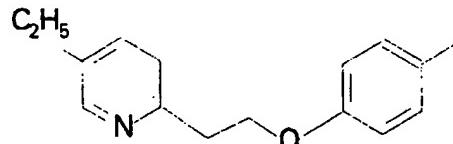


(b)

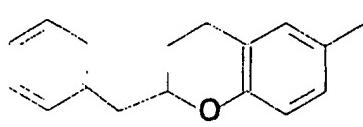
15



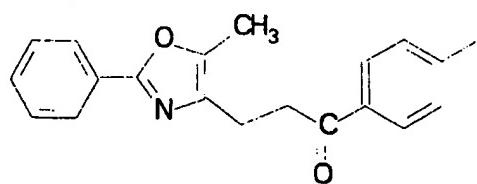
(c)



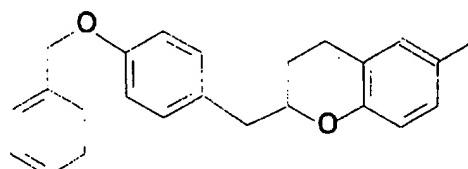
(d)



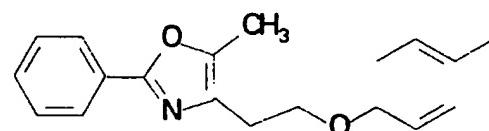
(e)



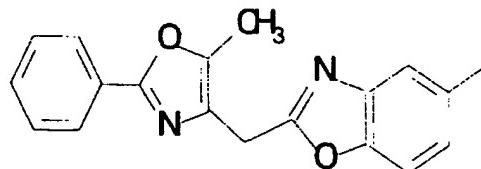
(f)



(g)



(h), and



(i)

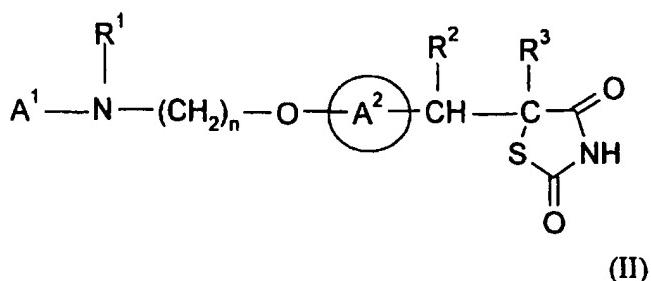
5 In particular should be mentioned the moieties of formula (a), (b), (c), (d) and (e).

Also included in the treatment of the invention are the thiazolidinediones and /or PPAR γ agonists disclosed in European Patent Applications, Publication Numbers: 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 10 0208420, 0177353, 0319189, 0332331, 0332332, 0528734 and 0508740, International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 5478852. The contents of these publications are included herein by reference.

Particular examples of thiazolidinediones are those disclosed in EP 0306228
15 and WO94/05659.

Further particular examples are the thiazolidenediones disclosed in EP0139421 and USP 5478852.

The compounds of EP 0306228 and WO94/05659 particularly include the compounds of formula (II):

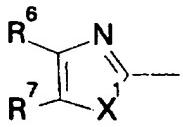


- or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or
 5 a pharmaceutically acceptable solvate thereof, wherein:
 A¹ represents a substituted or unsubstituted aromatic heterocycl group;
 R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group,
 wherein the aryl moiety may be substituted or unsubstituted, or a substituted or
 unsubstituted aryl group;
 10 R² and R³ each represent hydrogen, or R² and R³ together represent a bond;
 A² represents a benzene ring having in total up to five substituents; and
 n represents an integer in the range of from 2 to 6; to a human or non-human mammal
 in need thereof.

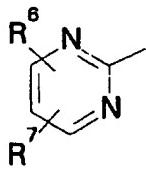
Suitable values for A¹ when it represents a 5- membered aromatic
 15 heterocycl group include thiazolyl and oxazolyl, especially oxazolyl.

Suitable values for A¹ when it represents a 6- membered aromatic
 heterocycl group include pyridyl or pyrimidinyl, especially pyridyl.

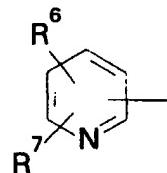
Preferably, A¹ represents a moiety of formula (j), (k) or (l):



(j)



(k)



(l)

20

wherein:

- R⁶ and R⁷ each independently represents a hydrogen or halogen atom, an alkyl or
 alkoxy group or a substituted or unsubstituted aryl group or when R⁶ and R⁷ are each
 attached to adjacent carbon atoms, then R⁶ and R⁷ together with the carbon atoms to
 25 which they are attached form a benzene ring wherein each carbon atom represented

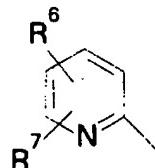
by R⁶ and R⁷ together is substituted or unsubstituted; and in the moiety of formula (j) X¹ represents oxygen or sulphur.

Aptly, A¹ represents a moiety of the above defined formula (j).

Aptly, A¹ represents a moiety of the above defined formula (k).

5 Aptly, A¹ represents a moiety of the above defined formula (l).

A particular form of moiety (l) is a moiety (l'):

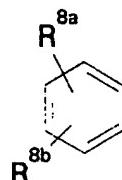


(l')

10

wherein R⁶ and R⁷ are as defined in relation to formula (l).

In one favoured aspect R⁶ and R⁷ together represent a moiety of formula (m):



(m)

15

wherein R^{8a} and R^{8b} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

Suitably, R^{8a} and R^{8b} each independently represent hydrogen, halogen, alkyl or alkoxy. Favourably, R^{8a} represents hydrogen. Favourably, R^{8b} represents hydrogen. Preferably, R^{8a} and R^{8b} both represent hydrogen.

In a further favoured aspect R⁶ and R⁷ each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R⁶ and R⁷ each independently represent hydrogen, alkyl or phenyl.

25 Preferably, for the moiety of formula (j), R⁶ and R⁷ together represent the moiety of formula (m).

Preferably, for the moieties of formula (k), (l) or (l'), R⁶ and R⁷ both represent hydrogen.

It will be appreciated that the five substituents of A² include three optional substituents. Suitable optional substituents for the moiety A² include halogen, substituted or unsubstituted alkyl or alkoxy.

Further suitable, favoured and preferred values for variables A², R¹, R², 5 R³ and n are as defined in EP 0306228 and WO94/05659.

A specific example of a compound of formula (II) is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, including those salts disclosed in WO94/05659 and most especially a maleic acid salt thereof, and/or a 10 pharmaceutically acceptable solvate thereof.

As indicated above, a compound of formula (I) may exist in one of several tautomeric forms, all of which are encompassed in the method of the present invention. It will be appreciated that the present invention encompasses the administration of all of the isomeric forms of the compounds of formula (I) and the 15 pharmaceutically acceptable salts thereof, including any stereoisomeric forms thereof, whether as individual isomers or as mixtures of isomers.

Further particular thiazolidinediones are those disclosed in EP0139421 and USP5478852, being of formula (I) as defined above wherein moiety T represents the above defined moiety (Ic), especially, (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione 20 (or troglitazone), 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione (or ciglitazone), 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione (or pioglitazone) or 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl]thiazolidine-2,4-dione (or englitazone)

25 The suitable, favoured and preferred thiazolidinediones disclosed in European Patent Applications, Publication Numbers: 0306228, 0008203, 0139421, 0032128, 0428312, 0489663, 0155845, 0257781, 0208420, 0177353, 0319189, 0332331, 0332332, 0528734, 0508740, International Patent Application, Publication Numbers 92/18501, 93/02079, 93/22445 and United States Patent Numbers 5104888 and 30 5478852 are those compounds defined as suitable, favoured and preferred in the respective patent publications.

The suitable, favoured and preferred acyclic insulin sensitizers disclosed in International Patent Applications, Publication Numbers WO91/19702, WO92/03425, WO93/21166 and WO94/01420 and United States Patent Number 52329452 are

those compounds defined as suitable, favoured and preferred in the respective patent publications.

Other suitable, favoured and preferred insulin sensitisers are the suitable, favoured and preferred compounds disclosed in European Patent Application,

- 5 Publication Number 0533933, International Patent Application, Publication Number WO 93/02079 , Japanese Patent Application Publication Number 05271204 and United States Patent Number 52644515 and 5478852.

Also specifically included in the method of the invention are the specific examples disclosed in the above mentioned patent applications.

- 10 Suitable pharmaceutically acceptable forms of leptin and/or an analogue, such as an agonist, thereof and/or agents which mimic or increases the pharmacological effect of leptin are as described in GB 2292382. The disclosures of GB 2292382 are incorporated herein by reference.

- 15 It will be appreciated that the treatment of the invention does not include treatment of disorders associated with overeating, such as obesity caused by overeating and bulimia when such treatment includes the administration as the sole medicament of a compound of the above defined compound of formula (II), including 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof.

- 20 When used herein the term 'leptin sensitiser' relates to a substance which increases the pharmacological response of, for example, a target cell, to a given plasma concentration of leptin.

- 25 A 'selective leptin sensitiser' functions so as to be substantially free from certain effects, such as the reduction of plasma concentrations of leptin or the reduction in the expression or secretion of leptin, especially when these effects arise from action in adipose tissue.

When used herein the term 'leptin resistant' relates to the condition wherein an individual has a lower than normal pharmacological response to leptin, for example due to a decreased response of target cells to a given plasma concentration of leptin.

- 30 An 'analogue of leptin' includes an agonist thereof and the analogues disclosed in GB 2292382.

- 35 When used herein the term 'PPAR γ agonist' relates to an agonist, such as a small molecular weight agonist, of the peroxisomal proliferator-activated receptor of the gamma subtype, this nuclear receptor is a member of the ligand activated transcription factor family that include the steroid, retinoid and thyroid receptors.

PPAR γ agonist activity may be assessed by use of the methodology disclosed by Lehmann et al : Journal of Biological Chem., 270, 12953-12956 (1995).

- When used herein 'treatment of obesity' includes medical or cosmetic treatments which are intended to result in body weight reduction. Of particular
5 importance is the obesity associated with the diabetes syndrome.

When used herein the term 'aryl' includes phenyl and naphthyl optionally substituted with up to five, preferably up to three, groups selected from halogen, alkyl, phenyl, alkoxy, haloalkyl, hydroxy, amino, nitro, carboxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkylcarbonyloxy, or alkylcarbonyl groups.

- 10 Suitable heterocyclyl groups are aromatic and non-aromatic heterocyclic groups.

Suitable non-aromatic heterocyclic groups include groups comprising single or fused ring heterocyclic groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen, optionally fused to one or more aryl groups.

- 15 Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

- 20 Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 5 to 7 ring atoms, preferably 5 or 6 ring atoms.

In particular, the aromatic heterocyclyl groups comprise 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

- 25 Suitable substituents for the heterocyclyl include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they are attached, may form an aryl group, preferably a benzene ring, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

- 30 It will be appreciated that where the above mentioned definitions of 'aryl', 'heterocyclyl' and the substituents thereof differ from those in the above mentioned patent publications with respect to the particular compounds disclosed therein, that the definitions in the said publications prevail.

When used herein the term 'halogen' refers to fluorine, chlorine, bromine and iodine; preferably chlorine.

When used herein the terms 'alkyl' and 'alkoxy' relate to groups having straight or branched carbon chains, containing up to 12 carbon atoms.

When used herein the term 'acyl' includes alkylcarbonyl groups.

Suitable alkyl groups are C₁-12 alkyl groups, especially C₁-6 alkyl groups

5 e.g. methyl, ethyl, n-propyl, iso-propyl, n-butyl, isobutyl or tert-butyl groups.

Suitable substituents for any alkyl group include those indicated above in relation to the term "aryl".

Suitable pharmaceutically acceptable salts include salts of carboxy groups and acid addition salts.

10 Suitable pharmaceutically acceptable salts of carboxy groups include metal salts, such as for example aluminium, alkali metal salts such as lithium, sodium or potassium, alkaline earth metal salts such as calcium or magnesium and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy alkylamines such as 2-hydroxyethylamine,

15 bis-(2-hydroxyethyl)-amine or tri-(2-hydroxyethyl)-amine, cycloalkylamines such as bicyclohexylamine, or with procaine, dibenzylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, N,N'-bisdehydroabietylamine, glucamine, N-methylglucamine or bases of the pyridine type such as pyridine, collidine, quinine or quinoline.

20 Suitable acid addition salts include pharmaceutically acceptable inorganic salts such as the sulphate, nitrate, phosphate, borate, hydrochloride and hydrobromide and pharmaceutically acceptable organic acid addition salts such as acetate, tartrate, maleate, citrate, succinate, benzoate, ascorbate, methane-sulphonate, α-keto glutarate and α-glycerophosphate, especially the maleate salt.

25 Suitable pharmaceutically acceptable solvates include hydrates.

The thiazolidinediones referred to herein are conveniently prepared using methods such as those disclosed in the, above mentioned, patent publications.

30 The PPAR γ agonists referred to herein are conveniently prepared according to the methods disclosed in the above mentioned patent publications in which they are disclosed: Thus a compound of formula (I), or the tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, may be prepared using the processes described in EP 0306228 and WO94/05659. Also for example, troglitazone may be prepared as described in EP0139421 or USP 5478852.

The salts and/or solvates of the thiazolidinediones may be prepared and isolated according to conventional procedures for example those disclosed in the, above mentioned, patent publications.

5 The present invention also provides a leptin sensitiser or a pharmaceutically acceptable derivative thereof, for use in the treatment and/or prophylaxis of leptin resistance and/or conditions associated with leptin resistance and/or complications thereof.

10 The present invention also provides a leptin sensitiser or a pharmaceutically acceptable derivative thereof, for use in the manufacture of a medicament for the treatment and/or prophylaxis of leptin resistance and/or conditions associated with leptin resistance and/or complications thereof.

In the above mentioned method the leptin sensitiser, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

15 In the treatment of the invention, the leptin sensitisers mentioned herein are formulated and administered in accordance with the methods disclosed in the above mentioned patent applications and patents.

20 Accordingly, the present invention also provides a pharmaceutical composition for the treatment and/or prophylaxis of obesity, which composition comprises a leptin sensitiser, or a pharmaceutically acceptable derivative thereof, and a pharmaceutically acceptable carrier therefor.

25 As indicated above it is preferred if medicament or also comprises an effective, non-toxic and pharmaceutically acceptable amount of leptin and/or an analogue, such as an agonist, thereof and/or an agent which mimics or increases the pharmacological effect of leptin.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarian acceptable salt.

30 The composition may, if desired, be in the form of a pack accompanied by written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

- In accordance with conventional pharmaceutical practice the carrier may
5 comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate, sodium lauryl sulphate or sucrose.

- 10 Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg, preferably 0.5 to 10 mg.

- Conveniently, the active ingredient may be administered as a pharmaceutical
15 composition herein before defined, and this forms a particular aspect of the present invention.

- In the above mentioned methods the active compound is taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and
20 more usually about 1 to 1500 mg, generally about 0.5 to 10 mg. That is in the range of from 1.429×10^{-3} to 85.714 mg/kg/day, more usually about 1.429×10^{-2} to 21.429 mg/kg/day, generally about 7.143×10^{-3} to 0.1429 mg/kg/day.

- 25 In a further aspect, the invention provides a novel leptin sensitiser, in particular a leptin sensitiser which does not include any of the compounds disclosed in the abovementioned patents and patent applications, such as the specific examples thereof.

No unacceptable toxicological effects are expected when the method of the invention is carried out within the above mentioned dosage ranges.

- The efficacy of active compounds in the present invention may be
30 demonstrated by use of conventional methodology, for example the test procedures disclosed in European Patent Number 0023385 or GB 2292382.

Pharmacological Data

The effects of the thiazolidinedione insulin sensitisier, BRL 49653, on plasma leptin concentrations and on epididymal fat *obmRNA* expression were examined in high fat-fed and high carbohydrate-fed adult Wistar rats. Feeding rats a high fat diet is known to induce insulin resistance (Storlein et al 1991, Diabetes 40:280-289). Diets were given for 4 weeks, with BRL 49653 (10 μ mol/kg/day) administered by an oral gavage for the last 4 days. Treatment with BRL 49653 reduced plasma leptin concentrations in high fat-fed rats from 2.34 ± 0.19 to 1.42 ± 0.09 ng/ml ($p < 0.001$). Plasma leptin was unaffected by BRL 49653 in the high-carbohydrate fed rats. There was no difference in *ob* mRNA expression between high fat-fed and high carbohydrate-fed rats with or without treatment. BRL 49653 had no effect on body weight gain or food intake (Table 1). The observation that BRL 49653 reduces circulating leptin but has no effect on food intake and body weight gain in insulin resistant rats suggests that the compound enhances cellular responses to leptin

15

Table 1: Body weights and food intakes of rats fed HF or HC diet \pm treatment.

	High Fat		High carbohydrate	
	control	BRL 49653	control	BRL 49653
Body weight (g) (start of treatment)	378.3 ± 7.1	378.3 ± 6.6	353.1 ± 8.3	366.0 ± 6.5
Body weight (g) (end of treatment)	392.1 ± 5.8	390.3 ± 6.4	364.0 ± 9.6	380.3 ± 5.8
Food intake during treatment (g/animal/day)	17.66 ± 0.64	17.60 ± 0.33	$25.91 \pm$ 1.41	24.88 ± 0.91
Metabolisable energy of diet (Kcal/animal/day)	78.39 ± 2.84	78.14 ± 1.45	$83.18 \pm$ 4.53	79.86 ± 2.93

20

Table 2: Fasting plasma measurements of rats fed HF or HC diet \pm treatment.

25

	High fat		High carbohydrate	
	Control	BRL 49653	Control	BRL 49653
leptin (ng/ml)	2.34 ± 0.19	$^{***} 1.42 \pm 0.09$	2.10 ± 0.11	1.91 ± 0.09

*** p < 0.001 HF-fed treated vs HF-fed control

Table 3: *ob* mRNA expression in HF-fed and HC-fed rats ± treatment.

Integrated Intensity	High Fat		High Carbohydrate	
	Control	BRL 49653	Control	BRL 49653
<i>ob</i>	0.89 ± 0.27	1.11 ± 0.28	1.00 ± 0.29	1.15 ± 0.22

5

MATERIALS AND METHODS

Animals: Adult male Wistar rats (175-200g) obtained from Charles River, UK, were allowed free access to food and water and were housed in a temperature controlled room at 21 °C ± 2 °C, relative humidity 55% ± 10%, under a 12 hour light:12 hour dark cycle (lights on at 06:00-18:00).

Diets: Rats were divided into two groups, one group were fed on a HF diet for 4 weeks and one group were fed on a high carbohydrate (HC) diet for 4 weeks. The HF diet contained (by weight) 30.7% casein, 7.5% fibre, 7.2% polyunsaturated fat, 35.2% saturated fat and 10.4% corn starch. The HC diet contained 21.2% casein, 3.3% fibre, 5.0 % polyunsaturated fat and 61.8% corn starch.

The metabolisable energy of the HF diet was 4440 Kcals/kg and for the HC diet was 3210 Kcals/kg. For the HF diet, the % metabolisable energies were 20% from protein, 12 % from carbohydrate and 68% from fat. The corresponding values for the HC diet were 20% from protein, 68% from carbohydrate and 12% from fat.

- Treatment:** After 3 weeks the rats fed on the HF diet were divided into two groups. The control group were given the dosing vehicle (1.0ml/kg body weight) daily for 4 days and the treated group received an oral dose of the antihyperglycaemic thiazolidinedione BRL 49653 daily for 4 days (10umol/kg). The rats fed the HC diet were similarly divided into two groups.
- The rats continued to receive their respective diets during the four day treatment period. Body weight and food and water intakes were recorded. On the 5th day, rats were fasted for 6 hours starting at 08:00 and at 14:00 they were anaesthetised with sodium pentobarbitone. Blood was collected from the dorsal aorta, anticoagulated with EDTA and plasma was stored at - 20 °C for leptin determination. The rats were

killed, the epididymal fat pads were removed, immediately freeze clamped and stored at -80 °C.

- 5 Plasma Measurements: Leptin concentrations were measured by immunoassay using recombinant murine leptin as standard, (rabbit anti-leptin IgG was raised to recombinant murine leptin, biotinylated and detected by incubation with europium-streptavidin and subsequent fluorescence).

- 10 Total RNA extraction and northern analysis: Total RNA was extracted (17) and the integrity of the RNA was checked on a 1.1 % agarose gel before northern analysis was performed. 20 ug total RNA was loaded on to a 1.1% denaturing formaldehyde gel and separated by electrophoresis at 150mA for 3 hours.

The gel was washed twice for 10 minutes at room temperature in 2 X SSC. The RNA was blotted by capillary transfer onto a positively charged nylon membrane overnight. After the transfer the RNA samples were fixed to the membrane by UV-crosslinking.

- 15 Probe labelling: Digoxigenin-11-UTP was incorporated into cDNA for *ob* and b-actin via PCR. b-actin was used to normalise the RNA in each sample.

- 20 Hybridisation: Prehybridisation was carried out for one hour at 42 °C in prehybridisation buffer (DIG Easy Hyb, Boehringer Mannheim). The cDNA probe was denatured by boiling for 5 minutes, cooled on ice then added to fresh hybridisation buffer (DIG Easy Hyb, Boehringer Mannheim).

- 25 Immunological detection of DIG-labelled probes: After hybridisation the membrane was washed twice at room temperature (2 X SSC, 0.1% SDS) for 10 minutes each and twice at 48 °C (0.1 X SSC, 0.1% SDS) for 10 minutes each. The Boehringer Mannheim protocol for standard immunological detection was then followed for the subsequent blocking, washing and detection stages. The wet membranes were sealed in plastic bags and exposed to X-ray film at room temperature.

The films were analysed on a densitometer and the levels of *ob* mRNA were expressed relative to the amounts of b-actin present in all of the samples (integrated intensity).

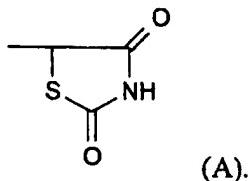
- 30 Data analysis: Results are expressed as mean ± SEM, n=9. The statistical significance of differences in means due to treatment or diet was determined using 2-way analysis of variance (ANOVA) and Students t-test.

CLAIMS

1. A method for the treatment and/or prophylaxis of leptin resistance and/or conditions associated with leptin resistance and/or complications thereof, in humans or non-human mammals, which method comprises the internal administration of an effective, non-toxic and pharmaceutically acceptable amount of a leptin sensitiser or a pharmaceutically acceptable derivative thereof.
- 10 2. A method according to claim 1, wherein the treatment is a prophylactic treatment.
3. A method according to claim 1 or claim 2, wherein the leptin sensitiser is a selective leptin sensitiser.
- 15 4. A method according to any one of claims 1 to 3, wherein the leptin sensitiser is administered in combination with leptin and/or an analogue, such as an agonist, thereof.
- 20 5. A method according to any one of claims 1 to 4, wherein the condition associated with leptin resistance is obesity.
6. A method according to claim 5, wherein the obesity is associated with or is caused by leptin resistance.
- 25 7. A method according to any one of claims 1 to 4, wherein the condition associated with leptin resistance is the insulin resistant diabetes syndrome.
8. A method according to claim 7 wherein the condition associated with leptin resistance is the pre-diabetic, impaired glucose tolerance phase of insulin resistant diabetes syndrome.
- 30 9. A method according to any one of claims 1 to 8, wherein the leptin sensitiser is an insulin sensitiser.

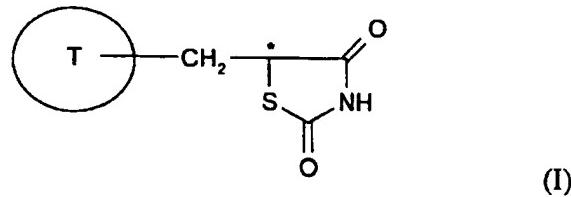
10. A method according to any one of claims 1 to 8, wherein the leptin sensitiser is a PPAR γ analogue, such as an agonist,
11. A method according to any one of claims 1 to 8, wherein the leptin sensitiser
5 is a glitazone.
- 12 A method according to any one of claims 1 to 8, wherein the leptin sensitiser is a compound comprising a moiety of formula (A):

10



15

13. A method according to claim 12, wherein the compound comprising a moiety of formula (A) is a compound of formula (I):

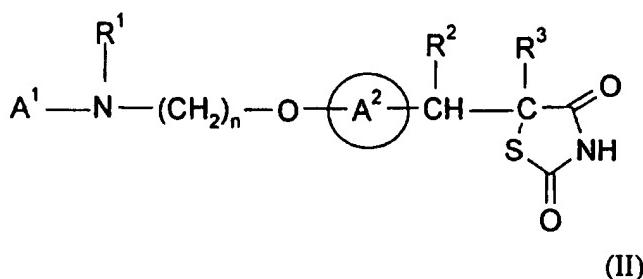


20

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, wherein T represents an aryl or heterocyclyl group optionally substituted with one or more alkyl groups, aralkyl groups or heterocyclalkyl groups, the said alkyl, aralkyl and heterocyclalkyl groups themselves being optionally substituted.

25

14. A method according to claim 12 or claim 13, wherein the compound comprising a moiety of formula (A) is a compound of formula (II):



- or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or
 5 a pharmaceutically acceptable solvate thereof, wherein:
- A¹ represents a substituted or unsubstituted aromatic heterocycl group;
- R¹ represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group, wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group;
- 10 R² and R³ each represent hydrogen, or R² and R³ together represent a bond;
- A² represents a benzene ring having in total up to five substituents; and
- n represents an integer in the range of from 2 to 6; to a human or non-human mammal in need thereof.
- 15 15. A method according to claim 12 or claim 13, wherein the compound comprising a moiety of formula (A) is:
 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione;
 (+)-5-[[4-[(3,4-dihydro-6-hydroxy-2,5,7,8-tetramethyl-2H-1-benzopyran-2-yl)methoxy]phenyl]methyl]-2,4-thiazolidinedione;
- 20 5-[4-[(1-methylcyclohexyl)methoxy]benzyl] thiazolidine-2,4-dione;
 5-[4-[2-(5-ethylpyridin-2-yl)ethoxy]benzyl] thiazolidine-2,4-dione; or
 5-[(2-benzyl-2,3-dihydrobenzopyran)-5-ylmethyl] thiazolidine-2,4-dione; or a pharmaceutically acceptable derivative thereof.

25

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/01928

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 6 A61K31/425 A61K31/44 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
 IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 139 421 A (SANKYO CO) 2 May 1985 cited in the application *cf. abstract, page 81, last para. bridging with page 82, first para.* ---	1-15
X	WO 94 05659 A (SMITHKLINE BEECHAM PLC ;POOL COLIN RIPLEY (GB); ROMAN ROBIN SHERWO) 17 March 1994 cited in the application *cf. abstract, page 5, lines 31-36, page 6, lines 4-7, claims 11-13*	1-15
X	WO 93 03724 A (UPJOHN CO) 4 March 1993 *cf. abstract, page 7, lines 30-33, claims 1,9 and 10* ---	1-15

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

1

Date of the actual completion of the international search

27 October 1997

Date of mailing of the international search report

13.11.97

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl.
Fax: (+31-70) 340-3016

Authorized officer

Stoltner, A

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 97/01928

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	C.B. CALLEN ET AL.: "Antidiabetic thiazolidinediones inhibit leptin (ob) gene expression in 3T3-L1 adipocytes" PROC. NATL. ACAD. SCI. USA, vol. 93, June 1996, pages 5793-5796, XP000615538 *see abstract and introduction on page 5793, also discussion at page 5795* -----	1-15

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 97/01928

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0139421 A	02-05-85	JP 1604002 C JP 2031079 B JP 60051189 A AU 570067 B AU 3255984 A CA 1263395 A DE 3470742 A DK 415184 A,B IE 58036 B MX 9203564 A US 4572912 A	22-04-91 11-07-90 22-03-85 03-03-88 07-03-85 28-11-89 01-06-88 01-03-85 16-06-93 01-09-92 25-02-86
WO 9405659 A	17-03-94	AU 674880 B AU 4973093 A CA 2143849 A CN 1101911 A CZ 9500565 A EP 0658161 A FI 951004 A HU 72639 A JP 8501095 T MX 9305397 A NO 950852 A NZ 255505 A PL 307812 A SI 9300452 A SK 27795 A ZA 9306509 A	16-01-97 29-03-94 17-03-94 26-04-95 15-11-95 21-06-95 03-03-95 28-05-96 06-02-96 31-01-95 03-03-95 22-08-97 26-06-95 30-06-94 09-08-95 16-06-94
WO 9303724 A	04-03-93	AT 151634 T AU 2479492 A DE 69219136 D DE 69219136 T EP 0601001 A ES 2101866 T JP 5510286 T	15-05-97 16-03-93 22-05-97 28-08-97 15-06-94 16-07-97 17-11-94